REMARKS

I. Prosecution History

The present application, containing 77 claims, was filed with a preliminary amendment canceling claims 1-7, 9-11 and 49-51. In the outstanding Office Action, claims 45-48 and 73 are pending and claims 8, 12-48, 52-72 and 74-77 were withdrawn from consideration as being drawn to a non-elected invention.

II. Preliminary Remarks

In paragraph 3 of the Action, the Examiner indicated that the amendment filed on October 27, 2000 did not have an adequate top margin, and required the Applicants to submit an amendment replacing claims 35 and 45. In the foregoing amendment, claim 35 was cancelled and claim 45 has been amended. To ensure that the originally filed claims are legible in the record, a copy of claims 35 and 45, as amended on October 27, 2000, is attached as Appendix C.

In paragraph 4 of the Action, the Examiner indicated claims 47 and 48 are in improper dependent form as they do not require the "isolated and purified polypeptide" of claim 8. Claims 45 and 46, from which claim 47 depends, have been amended to be independent form and do not recite an isolated and purified polypeptide of SEQ ID NO: 14. Claim 48 has been canceled and the claim objection to claim 48 has been rendered moot. Therefore, the objections to claims 47 and 48 should be withdrawn.

III. The Rejection under 35 U.S.C. §§ 101 and 112, first paragraph for lack of utility should be withdrawn.

In paragraph 5 of the Action, the Examiner rejected claims 45-48 and 73 under 35 U.S.C. § 101 for allegedly being drawn to an invention with no apparent or disclosed specific and substantial utility. In addition, due to the alleged lack of a specific or substantial utility, the examiner also rejected claims 45-48 and 73 under 35 U.S.C. § 112, first paragraph, stating one of skill in the art would not know how to make and use the claimed invention. The Applicants respectfully traverse these rejections.

A. GPCR proteins have a well established utility.

Many medically significant biological processes are mediated by signal transduction pathways involving G-proteins and other second messengers, and G protein coupled seven transmembrane receptor (GPCR) proteins are recognized as important therapeutic targets for a wide range of diseases. According to a recently issued United States patent, nearly 350 therapeutic agents targeting GPCRs have been successfully introduced onto the market in only the last fifteen years. (*See* Exhibit 1, U.S. Patent No. 6,114,127, at col. 2, lines 45-50.) A recent journal review reported that most GPCR ligands are small and can be mimicked or blocked with synthetic analogues. That, together with the knowledge that numerous GPCRs are targets of important drugs in use today, make identification of GPCRs "a task of prime importance." (*See* Exhibit 2, Marchese *et al., Trends Pharmacol. Sci.*, 20(9): 370-5, 1999.) Thus, the allegations that there is no well established utility for proteins of the class that the Applicants are now claiming is *directly refuted by industry evidence*. In this respect, the G protein coupled receptor family is analogous to the chemical genus that was the subject of *In re Folkers*, 145 USPQ 390 (CCPA 1965) (Compound that belongs to class of compounds, members of which are recognized as useful, is considered useful under §101.) The Patent Office does not serve the public by attempting to substitute a formulaic analysis of §101 for the established judgment of the biopharmaceutical industry as to what is "useful." If the Patent Office is aware of any literature from the industry suggesting that GPCR's are not useful, the Applicants request that it be made of record.

Likewise, the historical success in the industry at developing therapeutics targeted to GPCR proteins supports a conclusion that the specific and substantial utilities for CON202, discussed in the next sections below, are entirely credible.

B. Orphan Receptors have been considered useful by the Patent Office.

The Examiner stated that the instant specification does not disclose a specific biological role for CON202. The Examiner further states CON202 is undoubtedly an "orphan receptor" and therefore it is unclear what practical benefit the public can derive from the ligand unless the ligand is identified. However, in paragraph 9 of the Action, the Examiner cites U.S. Patent No. 6,071,722 (Elshourbagy *et al.*), which contains issued claims to a polynucleotide sequence that encodes the AXOR-1 polypeptide that is identical to the amino acid sequence of SEQ ID NO: 14 of the present invention. The disclosure in

Elshourbagy *et al.* does not demonstrate a biological activity or identify a ligand for the AXOR-1 polypeptide, although the Patent Office found claims to the polynucleotide sequence and variants thereof allowable. Assumingly, for patent claims to this polynucleotide sequence to have been issued, it must have a specific, substantial and credible utility.

If the U.S. Patent Office has determined that the polynucleotide sequence encoding the CON202 polypeptide is useful, the methods claimed in the present application also have a specific, substantial and credible utility. There is no question that the Applicants assert an utility in the specification and since the Patent Office has previously found the polynucleotide encoding the polypeptide of the invention useful, the rejections under 35 U.S.C. § 101 should be withdrawn.

C. Screening for ligands of CON202 taught in the application is a specific and substantial utility.

The Examiner stated that the practical benefit of identifying ligands of CON202 is unclear and therefore the claimed methods do not have a specific and substantial utility. The use of a particular receptor, such as CON202, to identify materials which specifically bind to that receptor is a specific utility because the method is not applicable to the general class of receptors. The method (which uses CON202 as a reagent) only identifies binding compounds for CON202, and cannot be expected to identify compounds that bind any other receptor. Stated differently, the identification of ligands which specifically bind to CON202 cannot be carried out with any integral membrane protein, but rather can only be carried out with CON202, if one hopes to have any reasonable expectation of success. The family of GPCRs is large, and the use of any other GPCR would not be expected to identify a ligand for CON202. Thus, a "specific" utility exists for CON202 polypeptides.

D. The polynucleotide of the invention is associated with Schizophrenia.

The Examiner stated that "there is absolutely no evidence of record or any line of reasoning that would support a conclusion the a protein of the instant invention is associated in any way with a disease or disorder to the brain." The Applicants dispute this statement. Chromosomal localization studies revealed that the polynucleotide sequence of SEQ ID NO: 13, which encodes the amino acid sequence of SEQ ID NO: 14, localized to chromosome 7 and was most nearly linked to the Stanford marker SHGC-12021 (position 7q21). Schizophrenia is linked to chromosome 7q22 and any genes localized to this region

are candidates for involvement or susceptibility of schizophrenia. (See page 133, line 28 through page 134 line 5 and Ekelund *et al.*, *Human Mol. Genetics*, 9(7): 1049-1057, 2000). To substantiate that CON202 polynucleotide is associated with schizophrenia, the CON202 mRNA transcript was detected within the cortical regions, lateral olfactory nuclei, hippocampus, subthalamic nucleus and the nigra-pars compacta of the rat brain. (See page 109, lines 3-6). The Applicants assert that there is a credible nexus between the polynucleotides and polypeptides of the invention and schizophrenia, and therefore the utility rejection should be withdrawn.

In view of the foregoing remarks, the Applicant submits that claims 46-48 and 73 demonstrate credible, specific, and substantial utility and respectfully request that the rejection of the claims under 35 U.S.C. §§ 101 and 112, first paragraphs, be withdrawn.

IV. The rejections under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

In paragraph 7 of the Office Action, the Examiner rejected claims 46, 48 and 73 under 35 U.S.C. § 112, first paragraph for containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to make and use the claimed invention. In particular, the Examiner stated that the specification does not identify any compounds which are capable as functioning as the recited "binding partner".

The specification does enable one of skill in the art to identify binding partners of CON202. To guide one of skill in the art, the specification sets out a list of molecule types that are known to bind GPCRs such as calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, ororants, and photons. (see page 2, lines 6-10). In addition, the specification teaches how to identify binding partners by forming a receptor/binding partner complex (see page 58, line 13 through page 59, line 24). The specification teaches one of skill in the art how to generate antibodies specific for CON202. These antibodies would be considered binding partners for CON202 and can be used to modulate the activity of the receptor and may be used in techniques to identify other binding partners of CON202. (See 55, line 22 through page 56, line 27).

The specification teaches *in vitro* assays using immobilized receptor polypeptides to identify binding partners (page 59, lines 3-17). The specification salso describes cell-based assays using cells which express the receptor polypeptide wherein

binding compounds are detected by monitoring cellular event such as calcium flux (page 59, lines 18-24). Furthermore, Example 6 teaches numerous techniques for monitoring the cellular events induced by GPCRs such as measuring cyclic AMP levels (page 120, line 5 through page 121, line 9), measuring intracellular calcium levels with aequorin (page 121, line 11 through page 122, line 16), monitoring activation of the transcription factor cAMP-response element, AP-1 or NFκB (page 122, line 18 through page 123, line 27), measuring intracellular calcium levels with FLIPR (page 123, line 28 through page 124, line 22), assaying mitogenesis (page 124, line 24 through page 125 line 19), monitoring hydrolysis of GTP/GDP (page 125, line 21 through page 126, line 24), evaluating MAP kinase activity (page 126, line 26 through page 127, line 30), measuring arachidonic acid release (page 128, lines 1-19), and monitoring extracellular changes in pH (page 128, line 21 through page 129, line 16).

In light of the foregoing remarks, the Applicants submit that the rejection of claims 46, 48 and 73 under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been overcome and should be withdrawn.

V. The rejections under 35 U.S.C. § 112, second paragraph, should be withdrawn.

In paragraph 8 of the Office Action, the Examiner rejected claim 73 under 35 U.S.C. § 112, second paragraph stating the term "CON202" is an indefinite limitation. The Applicants assert that the specification clearly identifies the molecule defined as CON202. However, the rejection has been rendered moot by cancellation of claim 73. This claim was canceled solely for the purpose of expediting prosecution, and without prejudice to the Applicant's right to seek broader claims in a continuing application. In light of the foregoing amendments, the Applicant requests the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

VI. The rejections under 35 U.S.C. § 102 (e) should be withdrawn.

In paragraph 9 of the Office Action, the Examiner rejected claims 45-48 and 73 as being anticipated by Elshourbagy *et al.* (U.S. Patent 6,071,722). The Examiner stated that the amino acid sequence of SEQ ID NO: 14 is identical to a sequence disclosed in Elshourbagy *et al.* and the patent contemplates the methods of the present invention. The Applicants traverse this rejection in light of the foregoing amendments.

Amended claim 45 is directed to assays for identifying CON202 binding partners that are isolated from brain tissue. The disclosure of Elshourbagy *et al.* does not provide any indication that the polypeptide is expressed in brain or that its binding partners would be present in brain tissue. Elshourbagy *et al.* solely provides a broad list of disease states contemplated to be associated with AXOR-1 activity, but does not contemplate the identity or the origin of possible ligands. Elshourbagy *et al.* does contemplate a role in neurological disorders, but the extensive list of disease states does not direct one of skill in the art to look to brain tissue for ligands and binding partners. (See Elshourbagy *et al.* column 2, line 60 through column 3, line 14). Therefore amended claim 45 is not anticipated by Elshourbagy *et al.*

Amended claim 46 is directed to methods of identifying modulators of binding between CON202 and its binding partners, wherein the modulators are selected in view of their ability to increase or decease binding to CON 2021 receptors expressed in mammalian neurons *in vivo*. Therefore, the claimed methods particularly identify modulator compounds that affect CON202 ligand binding *in vivo* as well as *in vitro*. The specification contemplates administering modulators of CON202 ligand binding in the neurons of mammals at page 30, lines 13-23. Elshourbagy *et al.* neither discloses or suggests this refined level of screening. Therefore amended claim 46 is not anticipated by Elshourbagy *et al.*

In response, the Applicants submit that the rejections based upon 35 U.S.C. § 102(e) should be withdrawn. The Applicant has amended claims 45 and 46 to distinguish their claimed invention from the disclosure of the cited document and cancelled claim 73 without prejudice.

CONCLUSION

In view of the amendment and remarks made herein, the Applicants believe claims 48-48 are in condition for allowance and request notification of the same.

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Respectfully submitted,

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APPENDIX A
MARKED UP VERSION OF THE AMENEDED CLAIMS

45. (Twice Amended) An assay to identify compounds isolated from brain tissue that bind a seven transmembrane receptor polypeptide, said assay comprising the steps of:

(a) contacting a composition comprising a seven transmembrane receptor polypeptide having an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 14 or a fragment thereof [according to claim 8] with a compound suspected of binding the seven transmembrane receptor polypeptide wherein the compound was isolated from brain tissue; and

(b) measuring binding between the compound and the seven transmembrane receptor polypeptide.

46. (Twice Amended) A method for identifying a modulator of binding between a seven transmembrane receptor polypeptide and a binding partner of the seven transmembrane receptor polypeptide, comprising the steps of:

(a) contacting the binding partner and a composition comprising the seven transmembrane receptor polypeptide in the presence and in the absence of a putative modulator compound, where the seven transmembrane receptor polypeptide [is a polypeptide according to claim 8] comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 14 or a fragment thereof and the binding partner is isolated from brain tissue;

(b) measuring binding between the binding partner and said seven transmembrane receptor polypeptide; [and]

(c) identifying a putative modulator compound in view of decreased or increased binding between the binding partner and seven transmembrane receptor polypeptide in the presence of the putative modulator, as compared to binding in the absence of the putative modulator;

(d) administering the putative modulator compound to a mammalian subject having neurons that express the seven transmembrane receptor polypeptide; and

(e) selecting a putative modulator compound in view of decreased or increased binding between the binding partner and seven transmembrane receptor polypeptide expressed in the mammalian neuron in the presence of the modulator, as compared to binding in the absence of the modulator.

47. (Twice Amended) An assay according to claim 45 or 46 wherein the composition comprises a cell expressing the seven transmembrane receptor polypeptide on its surface.

APPENDIX B

PENDING CLAIMS AFTER ENTRY OF THE AMENDMENT

45. (Twice Amended) An assay to identify compounds isolated from brain tissue that bind a seven transmembrane receptor polypeptide, said assay comprising the steps of:

(a) contacting a composition comprising a seven transmembrane receptor polypeptide having an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 14 or a fragment thereof with a compound suspected of binding the seven transmembrane receptor polypeptide wherein the compound was isolated from brain tissue; and

(b) measuring binding between the compound and the seven transmembrane receptor polypeptide.

46. (Twice Amended) A method for identifying a modulator of binding between a seven transmembrane receptor polypeptide and a binding partner of the seven transmembrane receptor polypeptide, comprising the steps of:

(a) contacting the binding partner and a composition comprising the seven transmembrane receptor polypeptide in the presence and in the absence of a putative modulator compound, where the seven transmembrane receptor polypeptide comprising an amino acids sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 14 or a fragment thereof and the binding partner is isolated from brain tissue;

(b) measuring binding between the binding partner and said seven transmembrane receptor polypeptide;

(c) identifying a putative modulator compound in view of decreased or increased binding between the binding partner and seven transmembrane receptor polypeptide in the presence of the putative modulator, as compared to binding in the absence of the putative modulator;

(d) administering the putative modulator compound to a mammalian subject having neurons that express the seven transmembrane receptor polypeptide; and

(e) selecting a modulator compound in view of decreased or increased binding between the binding partner and seven transmembrane receptor polypeptide expressed in the mammalian neuron in the presence of the modulator, as compared to binding in the absence of the modulator.

47. (Twice Amended) An assay according to claim 45 or 46 wherein the composition comprises a cell expressing the seven transmembrane receptor polypeptide on its surface.

48. An assay according to claim 47 wherein the measuring step comprises measuring intracellular signaling of the seven transmembrane receptor polypeptide induced by the compound.

APPENDIX C

CLAIMS 35 AND 45 AS AMENDED ON OCTOBER 27, 2002

35. (Amended) An antibody according to claim 31 that specifically binds an extracellular epitope of a seven transmembrane receptor having an amino acid sequence of SEQ ID NO: 14.

45. (Amended) An assay to identify compounds that bind a seven transmembrane receptor polypeptide, said assay comprising the steps of:

(a) contacting a composition comprising a seven transmembrane receptor polypeptide according to claim 8 with a compound suspected of binding the seven transmembrane receptor polypeptide; and

(b) measuring binding between the compound and the seven transmembrane receptor polypeptide.